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**Title:**

**PROCESS FOR MANUFACTURING A PHARMACEUTICAL CHEWING GUM**

**Abstract:**

The present invention provides a process for preparing a chewing gum tablet, in which a chewing gum composition is cooled to a temperature at which the composition is brittle, and the composition is ground while brittle to form a fine powder. In a preferred process, the composition is cooled by mixing with a coolant, such as solid carbon dioxide, and the mixture is ground to a powder. The powder can be mixed with a pharmaceutical active ingredient capable of topical absorption in the buccal cavity or in the mucous layer of the upper or lower intestinal tract, and formed into a tablet. Preferably, the mixture of the powder, pharmaceutical active ingredient, and other additives such as coating agents, binders, additional active ingredients, and sweeteners, are granulated in a fluidized bed granulator prior to forming the mixture into a tablet. The resulting tablet provides a dosage form of the pharmaceutical active ingredient having a more accurate and uniform dose of the active ingredient.

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(54) Title: PROCESS FOR MANUFACTURING A PHARMACEUTICAL CHEWING GUM

(57) Abstract: The present invention provides a process for preparing a chewing gum tablet, in which a chewing gum composition is cooled to a temperature at which the composition is brittle, and the composition is ground while brittle to form a fine powder. In a preferred process, the composition is cooled by mixing with a coolant, such as solid carbon dioxide, and the mixture is ground to a powder. The powder can be mixed with a pharmaceutical active ingredient capable of topical absorption in the buccal cavity or in the mucous layer of the upper or lower intestinal tract, and formed into a tablet. Preferably, the mixture of the powder, pharmaceutical active ingredient, and other additives such as coating agents, binders, additional active ingredients, and sweeteners, are granulated in a fluidized bed granulator prior to forming the mixture into a tablet. The resulting tablet provides a dosage form of the pharmaceutical active ingredient having a more accurate and uniform dose of the active ingredient.

**PROCESS FOR MANUFACTURING  
A PHARMACEUTICAL CHEWING GUM**

**FIELD OF THE INVENTION**

The present invention relates to processes for producing chewing gum tablets as dosage forms for pharmaceutical therapeutic agents, and in particular to a process for making a pharmaceutical chewing gum dosage form having a more accurate and uniform dose of the pharmaceutical active ingredient.

**BACKGROUND**

Pharmaceutical therapeutic agents, such as drugs, are formulated in a variety of dosage forms, depending upon the target absorption site of the drug, the intended time profile for absorption, the solubility characteristics of the drug, the susceptibility of the drug to various forms of attack in vivo, such as enzymatic degradation and organ uptake, and other considerations well-known to those skilled in the art. A large number of drugs are formulated in orally ingestible dosage forms for delivery into the gastrointestinal tract, where they are absorbed into the blood stream and carried to various organs or tissues where the pharmacological action is exerted. Typically, such dosage forms are capsules or tablets, which may further be provided with various coatings, to assist in passage through the gastrointestinal tract, or to provide a delayed or extended release profile. When more rapid therapeutic action is desired, or when the therapeutic agent is particularly susceptible to chemical or enzymatic attack in the gastrointestinal tract, a preferred route of delivery is injection into the blood stream, and the corresponding dosage form is an injectable liquid or solution. Still other drugs are delivered topically to the skin, eyes, and various mucosal tissues, in dosage forms such as ointments, creams, gels and lotions.

A number of therapeutically useful drugs are capable of buccal absorption; *i.e.*, absorption in the oral cavity, either sublingually or throughout the oral mucosal wall, or by dissolution in the saliva and absorption in the throat, esophagus, or upper gastrointestinal tract. For drugs having significant buccal and/or upper and lower gastrointestinal tract absorption, oral dosage forms taking advantage of the absorption, such as lozenges, chewable tablets, and chewing gum, are particularly advantageous. Such dosage forms permit more rapid therapeutic action compared to per-oral (swallowed) dosage forms, and the topically absorbed therapeutic agent also partially escapes liver metabolism.

1           The chewing gum dosage form is particularly attractive due to its ease of  
administration and the generally acceptable or even pleasant qualities of chewing gum.  
These attractive properties can significantly improve patient compliance with the dosage  
regimen. Thus, for example, U.S. Patent No. 4,971,079 is directed to chewing gum  
5       compositions having an anti-nicotine therapeutic effect, for use in facilitating cessation of  
smoking. Likewise, U.S. Patent No. 5,922,347 is directed to chewing gum compositions  
containing acetylsalicylic acid, a well-known anti-inflammatory and analgesic compound.

          The conventional chewing gum processing technology involves melting a gum  
base in, for example, a sigma blender, and adding components such as sweeteners and  
10       flavorants to the melt. The melted mass is then extruded, rolled into sheets, and cut to the  
desired shape on the rollers. This conventional technology, however, suffers from several  
disadvantages, when applied to the preparation of pharmaceutical chewing gum dosage  
forms. For example, the elevated temperatures used in the melt can adversely affect the  
chemical stability of the therapeutic agent contained therein. In addition, the melting and  
15       mixing process of the highly viscous gum mass makes controlling the accuracy and  
uniformity of the drug dose difficult, and this difficulty is further exacerbated by the lack  
of a precise form, shape or weight of the dosage form. Further, the gum processing  
technology is not easily adapted to incorporate the stringent sanitary manufacturing  
conditions required for production of pharmaceutical products, and the concomitant  
20       process validation and control measures. In addition, conventional gum processing  
technology is generally poorly suited for high-speed, more economical, production.

          Several patents are directed to improved methods of processing chewing gums, in  
order to overcome some of the disadvantages described above. U.S. Patent No. 4,000,321,  
for example, is directed to a process for preparing chewing gum, in which a chewing gum  
25       composition is cooled to -15 °C to facilitate fragmentation, and the cooled composition is  
pulverized with a crusher, hammer mill, pelletizer or turbomill. The pulverized product is  
then melted to cause the pulverized pieces to co-adhere, forming a chewing gum  
reportedly having low specific gravity and a soft chewing texture. The process, however,  
suffers from all of the disadvantages associated with heating, process speed, poorly  
30       defined dosage forms and weights described above, and is not well-suited for making a  
pharmaceutical chewing gum dosage form.

1 U.S. Patent No. 4,753,805 is directed to a chewing gum composition in the form of  
a tablet having a low moisture content. The tablet is produced by grinding a chewing gum  
composition, blending the ground composition with a compression aid, and compressing  
the granulated product to form a tablet. Grinding of the chewing gum composition,  
5 typically a difficult process because of the tendency for the gum to stick to the grinding  
apparatus, is accomplished by the use of 2-8% by weight of a grinding aid such as an  
alkaline metal phosphate, an alkaline earth metal phosphate, or a maltodextrin. The use of  
such grinding aids, however, is disadvantageous. The metal phosphate salts are highly  
alkaline, and such alkalinity may be incompatible with acidic ionizable therapeutic agents,  
10 for example. In addition, the grinding aid remains in the composition and ultimately in the  
chewing gum tablet, and the presence of a large amount of metal phosphate in the dosage  
form is potentially problematic from therapeutic and safety perspectives.

Thus, there is a need for processes to produce dosage forms of buccally absorbable  
therapeutic agents which do not suffer from the disadvantages of conventional  
15 pharmaceutical chewing gum formulations.

### **SUMMARY OF THE INVENTION**

The foregoing and other advantages are achieved by the process of the present  
invention, in which a chewing gum composition is cooled to a temperature at which the  
composition is brittle, and the composition is ground while brittle to form a fine powder.  
20 In a preferred process, the composition is cooled by mixing with a coolant, such as solid  
carbon dioxide, and the mixture is ground to a powder. The powder can be mixed with a  
pharmaceutical active ingredient capable of buccal and/or upper or lower gastrointestinal  
tract topical absorption (*i.e.*, topically effective toward the gastrointestinal tract), and  
formed into a tablet. Preferably, the mixture of the powder, pharmaceutical active  
25 ingredient, and other additives such as coating agents, binders, additional active  
ingredients, and sweeteners, are granulated in a fluidized bed granulator prior to forming  
the mixture into a tablet. The resulting tablet provides an improved dosage form of the  
pharmaceutical active ingredient.

Thus, in one aspect, the present invention provides a process for preparing a  
30 chewing gum tablet, the process including the steps of cooling a chewing gum  
composition to a temperature at which the composition is brittle, grinding the cooled

1 chewing gum composition, and forming the ground chewing gum composition into a tablet.

5 In another aspect, the present invention provides a process for preparing a chewing gum tablet, the process including the steps of providing a mixture including a chewing gum composition and solid carbon dioxide, grinding the mixture to form a powder, removing the solid carbon dioxide from the powder, and forming the powder into a tablet.

10 In another aspect, the present invention provides a process for preparing a dosage form of an active ingredient topically effective toward the gastrointestinal tract, the process including the steps of providing a mixture including a chewing gum composition and solid carbon dioxide, grinding the mixture to form a powder, removing the solid carbon dioxide from the powder, mixing the powder with a composition including the active ingredient to form an active ingredient-containing powder, granulating the active ingredient-containing powder in a fluidized bed granulator, and compressing the granules into a tablet to form a dosage form containing the active ingredient.

15 In another aspect, the present invention provides a chewing gum dosage form of an active ingredient topically effective toward the gastrointestinal tract, the dosage form including a gum base and an active ingredient and being formed of a plurality of compressed granules containing the gum base and active ingredient.

20 These and other objects and features of the present invention will become more fully apparent from the following description and appended claims, or may be learned by the practice of the invention as set forth hereinafter.

#### **DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS**

25 The present invention is directed to processes for improved production of pharmaceutical chewing gum dosage forms. The processes of the present invention enable production of chewing gum tablets without the disadvantages of heating the therapeutic agent, and without problems associated with inaccuracy and non-uniformity of therapeutic agent doses characteristic of conventional chewing gum processes. The present invention achieves these and other significant advantages by a process in which a chewing gum composition is cooled to a brittle temperature, ground while at a brittle temperature to form a powder, and formed into a tablet. The pharmaceutical therapeutic agent, or active ingredient, is readily mixed with the powdered gum composition prior to tablet formation,

30

1 to produce a uniform and accurate mixture, from which a well-defined and precise tablet dosage form can be prepared by tabletization.

5 In one step of the process of the present invention, a chewing gum composition is cooled to a temperature at which the composition is brittle. The chewing gum composition can be any chewing gum composition, such as conventional compositions known in the art. In general, such compositions include a chewing gum base, to which may be added flavorants, sweeteners, colorants, and other ingredients known in the art. The chewing gum base is typically a natural or synthetic elastomer, such as rubber, chicle, lechi caspi, jelutong, polyisobutylene, an isobutylene-isoprene copolymer, a styrene-10 butadiene copolymer, or other suitable gum base known in the art. In order to facilitate the subsequent grinding step, the chewing gum composition is preferably in the form of chips, pellets, or other relatively small particles.

15 The chewing gum composition is cooled to a temperature at which the composition is brittle. It should be appreciated that even a mildly cooled chewing gum composition will possess some degree of brittleness; however, to be suitable for the process of the present invention, the composition is cooled to a temperature at which the composition is sufficiently brittle such that the brittleness is maintained during the subsequent grinding step without adhesion to the grinding apparatus. The appropriate temperature is determined in part by the specific composition of the chewing gum, and is easily20 determined empirically by observing the properties of the cooled chewing gum composition. Thus, for example, a chewing gum composition cooled to a temperature sufficiently low can be ground in, for example, a mill grinder, without the composition sticking to the grinder parts. Preferably, the temperature will be less than -15 °C, more preferably less than -30 °C, and still more preferably less than about -40°C.

25 The cooling can be carried out by any of a variety of cooling processes. The chewing gum composition can be frozen in a conventional freezer apparatus capable of reaching the very low temperatures needed to achieve the requisite brittleness. Preferably, however, the chewing gum composition is cooled by contacting with a coolant. The coolant can be any substance capable of cooling the chewing gum composition to the30 desired temperature and can be, for example, a cryogenic liquid such as liquid nitrogen, a cold solid such as solid carbon dioxide, or a cold gas such as the gaseous boil-off from a cryogenic liquid. The coolant should be chosen so that the coolant does not interact

1 adversely with the chewing gum composition or with the mixing or grinding apparatuses  
used in the present process. In addition, the coolant should not produce a substance upon  
warming that suffers from such adverse interactions, or that leaves a residue that adversely  
affects subsequent processing or presents potential safety hazards when the chewing gum  
5 tablet is chewed. For example, a coolant such as water ice, even if cooled to a sufficiently  
low temperature, would not be preferred, as any water ice that melts will form liquid  
water, which is absorbed by the chewing gum composition. Likewise, a coolant such as a  
hydrocarbon slush would not be preferred, since any hydrocarbon residue remaining in the  
chewing gum composition would present potential safety hazards when the chewing gum  
10 tablet is consumed.

In accordance with the present invention, and in a particularly preferred aspect, it  
has been surprisingly found that by mixing a chewing gum composition with solid carbon  
dioxide (dry ice), the chewing gum composition can be cooled to a brittle temperature  
without the undesirable effects discussed above. At the sublimation temperature, -78.5 °C,  
15 solid carbon dioxide is sufficiently cold to ensure that the chewing gum composition is  
suitably brittle. Of course, the solid carbon dioxide can be cooled to an even lower  
temperature, if desired. Upon warming, the solid carbon dioxide sublimates to form carbon  
dioxide gas, which does not react with the chewing gum composition, is not absorbed by  
the composition, and does not interact adversely with processing apparatuses. Further, the  
20 gaseous, non-reactive nature of the sublimation product ensures that no undesirable and  
potentially hazardous residue of the coolant remains in the chewing gum tablet product.  
Preferably, the solid carbon dioxide coolant is provided in pelletized form to facilitate  
further processing steps.

Alternatively, the steps of cooling the chewing gum composition and grinding the  
25 composition can be combined into a single step by, for example, cooling the grinding  
apparatus itself, such as by contacting the grinding apparatus with a coolant. For example,  
in this alternative aspect, the grinding apparatus can be placed in a cooling jacket of liquid  
nitrogen or other cold liquid. For more efficient cooling, in this embodiment, the chewing  
gum composition is preferably pre-cooled, although the pre-cooling need not be to a  
30 temperature as low as the brittle temperature. It should be appreciated that even in the  
preferred embodiment, wherein the chewing gum composition is cooled by mixing with a  
coolant, it may also be advantageous to cool the grinding apparatus as well.



1        If desired, the chewing gum composition can be mixed with an anti-caking agent  
prior to the grinding step, and the use of an anti-caking agent is preferred. Such anti-  
caking agents are known in the art. A preferred anti-caking agent is precipitated silicon  
dioxide. In a preferred embodiment in which the chewing gum composition is mixed with  
5        solid carbon dioxide and an anti-caking agent prior to grinding, the anti-caking agent helps  
to prevent agglomeration of the subsequently ground chewing gum particles, upon  
sublimation of the solid carbon dioxide.

      If a coolant, such as solid carbon dioxide, and other components, such as an anti-  
caking agent are used, the chewing gum composition and other substances can be  
10       combined using a conventional mixing apparatus, such as a vented V-blender.

      The chewing gum composition, and other components such as coolant and anti-  
caking agent, are ground to form a fine powder. The grinding can be carried out using any  
conventional grinding apparatus, such as a mill grinder. In a preferred embodiment, a  
mixture of a chewing gum composition, solid carbon dioxide, and precipitated silica is  
15       provided, and the mixture is introduced into a mill grinder. In this embodiment, the  
mixture is ground to a fine powder, and the solid carbon dioxide remains present during  
the grinding process. It has been surprisingly found that by co-grinding the chewing gum  
composition and solid carbon dioxide, the chewing gum composition can be ground into a  
fine powder, without any adverse adhesion to the grinding apparatus.

20       The desired properties of the ground chewing gum composition are better achieved  
when the composition is kept at a very low temperature throughout the grinding process.  
Thus, in a particularly preferred process, a mixture of chewing gum composition, solid  
carbon dioxide and precipitated silica is ground in a mill grinder in a first grinding step,  
additional solid carbon dioxide and precipitated silica are added to the ground  
25       composition, and the composition is further ground in a second grinding step. This two-  
step grinding process advantageously keeps the chewing gum composition at a very low  
temperature. Although not wishing to be bound by theory, it is further believed that the  
presence of the solid carbon dioxide particles, in addition to providing the necessary  
cooling, also serves to enhance the efficiency of the grinding process. It should be  
30       appreciated that although a two-step grinding process is described herein, the number of  
steps is not particularly limited. Thus, a process in which additional solid carbon dioxide

1 and/or precipitated silica are added in multiple steps, or even in a slow, continuous stream, may also be used if desired.

After the composition is ground to a powder, the coolant can be removed by, for example, allowing the coolant to evaporate. Using the preferred coolant of solid carbon  
5 dioxide, the coolant is removed simply by allowing the solid carbon dioxide to sublime, releasing harmless carbon dioxide gas and leaving no undesirable contaminants. The ground composition can be stored such that the carbon dioxide gas can escape, as for example in loosely closed plastic bags. Alternatively, the carbon dioxide can be removed more rapidly by processing the ground composition in a fluidized bed reactor.

10 Once the coolant has been removed from the powder, the powder can be mixed with other ingredients as desired, before forming the powder into a tablet. Such ingredients can be any ingredient known to be incorporated into chewing gum and not incompatible with tablet formation, such as coating agents, binders, lubricants, sweeteners and the like. Preferably, a pharmaceutical active ingredient topically effective toward the  
15 gastrointestinal tract is added in an amount such that the tablet ultimately formed includes a therapeutically effective dose of the active ingredient. As used herein, the term "topically effective toward the gastrointestinal tract" means having significant absorption in the buccal cavity and/or the mucous layer of the upper and/or lower gastrointestinal tract. The active ingredient can be any active ingredient having such topical absorption,  
20 such as, for example, gastrointestinal anti-infective drugs, anti-diarrheal drugs, anti-cholic drugs, cardiovascular drugs such as nitroglycerin, and calcium channel blocking agents such as nifedipine.

Such ingredients can be combined with the powder by blending, in for example, a sigma mill, or a high shear mixer. If a conventional blending apparatus is used, the  
25 powder mixture should include sufficient amounts of binder to enable effective processing of the mixture. Such binders, well-known in the art, are typically aqueous, and the large amounts of aqueous binder necessary to enable tabletization from a blended mixture are not preferred, as the mixture tends to swell and to develop a disadvantageous stickiness that makes tabletization less efficient. However, although not preferred, such blending  
30 processes can still be used in the process of the present invention.

In a preferred process, it has been surprisingly found that the powdered chewing gum composition produced by the process described above can be combined with other

1 ingredients, such as coating agents, binders, sweeteners and active ingredients, in a  
fluidized bed reactor. The use of a fluidized bed reactor is particularly advantageous, as  
the process partially rebuilds the powder into granules, as well as coats the powder  
5 particles and/or granules with a coating agent, thereby minimizing undesired particle  
agglomeration. In this embodiment, the temperature of the process should be controlled.  
If the temperature is too low, the mixture (the "blend") will stick because of a low  
evaporation rate as the binding solution is sprayed on the blend. The granules that develop  
are then too large for subsequent tabletization. If the temperature is too high, the blend  
can soften, with the same disadvantageous results. With these considerations in mind, one  
10 skilled in the art can readily determine the appropriate process temperature by observing  
and optimizing the properties of the granules produced. To reduce the processing time,  
the fluid bed granulator can be pre-heated to the chosen processing temperature prior to  
adding the powder mixture. After granulation, the granulate can be discharged onto  
screens, and any granules that are too large can be removed.

15 In a preferred process, the powder mixture, containing the powdered chewing gum  
composition, active ingredient, and other additives, is weighed into individual "charges"  
for the fluid bed granulator. After processing as described above, and screening, the  
individual charges are then preferably recombined and mixed in a V-blender, and the  
resultant "cross-blend" is then discharged across a screen to again remove any granules  
20 that are too large. It is particularly advantageous to sample the cross-blend discharge by  
taking multiple samples from the discharge stream, for analysis of the active ingredient.  
Thus, the discharge mixture can be stored while the multiple samples are analyzed, to  
insure that the desired level and uniformity of level of active ingredient are present. If  
necessary, additional active ingredient can then be added.

25 The discharge mixture is again placed in a V-blender, and any additional active  
ingredient added. In addition, an anti-adherent is preferably added at this time, along with  
any other desired excipients or inactive ingredients. A preferred anti-adherent is talc. The  
mixture can then be discharged, again screened, and staged for compression.

30 Compression to form tablets can be carried out by any conventional process, such  
as a punching process. Of course, the punching process should be monitored for signs of  
sticking to the punches, and the apparatus cleaned, and/or coated with additional anti-  
adherent as needed.

1           In another aspect, the present invention is directed to chewing gum dosage forms  
of a pharmaceutical active ingredient topically effective toward the gastrointestinal tract,  
the dosage form being a tablet formed of compressed granules of a gum base and the  
active ingredient. The granules forming the tablet can be of a size convenient for  
5           tabletization, typically from about 15 to about 30 mesh size, and preferably about 20 to  
about 25 mesh size. The tablets can be produced by any of the methods described above.  
Advantageously, the tablet does not contain any residue of a grinding aid, such as an  
alkaline phosphate.

10           The present invention may be embodied in other specific forms without departing  
from its spirit or essential characteristics. The described embodiments are to be  
considered in all respects only as illustrative and not restrictive. The scope of the  
invention is, therefore, indicated by the appended claims rather than by the foregoing  
description. All changes which come within the meaning and range of equivalency of the  
claims are to be embraced within their scope.

15           What is claimed is:

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- 1 1. A process for preparing a chewing gum tablet, the process comprising:
- (a) cooling a chewing gum composition to a temperature at which the composition is brittle;
- 5 (b) grinding the cooled chewing gum composition; and
- (c) forming the ground chewing gum composition into a tablet.
2. The process of claim 1, wherein the step of cooling the chewing gum composition comprises contacting the composition with a coolant, wherein the coolant is a non-reactive substance capable of cooling the chewing gum composition to the brittle temperature.
- 10 3. The process of claim 2, wherein the coolant is solid carbon dioxide.
4. The process of claim 1, wherein the step of grinding the cooled chewing gum composition is carried out in the presence of a coolant in contact with the chewing gum composition, wherein the coolant is a non-reactive substance.
5. The process of claim 4, wherein the coolant is solid carbon dioxide.
- 15 6. The process of claim 1, wherein the steps of cooling and grinding are carried out by mixing the chewing gum composition with solid carbon dioxide and grinding the chewing gum and solid carbon dioxide mixture.
7. The process of claim 6, wherein the chewing gum composition is mixed with solid carbon dioxide and an anti-caking agent.
- 20 8. The process of claim 1, wherein the cooling and grinding steps are carried out by:
- (i) providing a mixture of the chewing gum composition, solid carbon dioxide, and an anti-caking agent;
- (ii) grinding the mixture in a first grinding step;
- 25 (iii) adding additional amounts of solid carbon dioxide and anti-caking agent to the ground mixture; and
- (iv) further grinding the mixture in a second grinding step.
9. The process of claim 8, wherein the anti-caking agent is precipitated silicon dioxide.
- 30 10. The process of claim 1, wherein the chewing gum composition is cooled to a temperature below -30 °C.

1           11.     The process of claim 1, wherein the chewing gum composition is cooled to a temperature below about -40 °C.

          12.     The process of claim 1, further comprising granulating the ground chewing gum composition before the step of forming tablets.

5           13.     The process of claim 12, wherein the step of granulating is carried out in a fluid bed granulator.

          14.     The process of claim 13, further comprising coating the chewing gum particles in the fluid bed granulator with a coating agent.

10           15.     The process of claim 1, further comprising mixing the chewing gum composition with an active ingredient topically effective toward the gastrointestinal tract.

          16.     A process for preparing a chewing gum tablet, the process comprising:

(a)     providing a mixture comprising a chewing gum composition and solid carbon dioxide;

(b)     grinding the mixture to form a powder;

15          (c)     removing the solid carbon dioxide from the powder; and

(d)     forming the powder into a tablet.

          17.     The process of claim 16, wherein mixture in step (a) further comprises an anti-caking agent.

20           18.     The process of claim 17, wherein the anti-caking agent is precipitated silicon dioxide.

          19.     The process of claim 17, wherein grinding step comprises:

(i)     grinding the mixture in a first grinding step;

(ii)    adding additional amounts of solid carbon dioxide and anti-caking agent to the ground mixture; and

25          (iii)   further grinding the ground mixture in a second grinding step to form a powder.

          20.     The process of claim 16, wherein the step of removing the solid carbon dioxide from the powder comprises storing the powder for a sufficient time such that substantially all of the solid carbon dioxide sublimes.

30           21.     The process of claim 16, wherein the step of removing the solid carbon dioxide from the powder comprises processing the powder in a fluid bed granulator.

1           22.     The process of claim 16, further comprising granulating the powder before the step of forming a tablet.

          23.     The process of claim 22, wherein the step of granulating is carried out in a fluid bed granulator.

5           24.     The process of claim 23, wherein the powder is mixed with a coating agent prior to the step of granulating.

          25.     The process of claim 16, further comprising mixing the powder with an active ingredient topically effective toward the gastrointestinal tract.

10           26.     A process for preparing a dosage form of an active ingredient topically effective toward the gastrointestinal tract, the process comprising:

(a)     providing a mixture comprising a chewing gum composition and solid carbon dioxide;

(b)     grinding the mixture to form a powder;

(c)     removing the solid carbon dioxide from the powder;

15           (d)     mixing the powder with a composition comprising the active ingredient to form an active-containing powder;

(e)     granulating the active-containing powder in a fluidized bed granulator

(f)     compressing the granules into a tablet to form a dosage form containing the active ingredient.

20           27.     The process of claim 26, wherein mixture in step (a) further comprises an anti-caking agent.

          28.     The process of claim 27, wherein the anti-caking agent is precipitated silicon dioxide.

25           29.     The process of claim 27, wherein grinding step comprises:

(i)     grinding the mixture in a first grinding step;

(ii)    adding additional amounts of solid carbon dioxide and anti-caking agent to the ground mixture; and

(iii)   further grinding the ground mixture in a second grinding step to form a powder.

30           30.     The process of claim 26, wherein the step of removing the solid carbon dioxide from the powder comprises storing the powder for a sufficient time such that substantially all of the solid carbon dioxide sublimes.

1           31.     The process of claim 26, wherein the step of removing the solid carbon dioxide from the powder comprises processing the powder in a fluid bed granulator.

          32.     The process of claim 26, wherein the composition in step (d) further comprises a coating agent.

5           33.     The process of claim 26, wherein the composition in step (d) further comprises at least one additive selected from the group consisting of binders, coating agents, sweeteners, and additional active ingredients.

          34.     A dosage form of a pharmaceutical chewing gum comprising a plurality of particles compressed to form a tablet, the particles comprising a chewing gum composition and a pharmaceutical active ingredient topically effective toward the gastrointestinal tract.

10           35.     The dosage form of claim 34, wherein the particles have an average size of about 15 to about 30 mesh.

          36.     The dosage form of claim 34, wherein the tablet is substantially free of a grinding aid or a grinding aid residue.



## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US00/15282

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) :A23G 3/30; A 61K 9/68

US CL :424/48, 440, 441; 426/3,5,285,454

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/48, 440, 441; 426/3,5,285,454

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
NONE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,711,961 A (REINER et al) 27 January 1998 (27.01.98), see entire document.	34,36 ----- 1-33, 35
Y	US 4,975,270 A (KEHOE) 04 December 1990 (04.12.90), see entire document.	1-33
A	US 4,803,082 A (CHERUKURI et al) 07 February 1989 (07.02.89).	1
A	US 4,405,647 A (FISHER et al) 20 September 1983 (20.09.83).	1
A	US 4,000,321 A (MOCHIZUKI et al) 28 December 1976 (28.12.76).	1

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

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